REMARKS

I. Status of Claims

Upon entry of the present amendment, claims 6-11 and 15-24 will remain pending in this application. Claims 6-11 are withdrawn as drawn to a non-elected invention, and claims 15-24 are under examination in this application.

Claims 15, 23, and 24 are presently amended to clarify their scope. Support for the claim amendments can be found throughout the application as filed, *inter alia*, in the Examples and at paragraphs [0017]; [0051]; [0052]; [0054]; and [0083] of the application as filed. The Examples describe a plurality of different antibodies (VA130, VB16, and VB157) that bind to a single antigen (Mpl) (see, page 19, lines 31-33 of the application as filed) and demonstrate that the minibody forms of these antibodies have an agonistic activity that is greater than that of the respective whole antibodies (see, Example 2.9 at pages 27-28 of the application as filed). No new matter is added.

II. Priority

Applicants note that although the "Office Action Summary" at section 12 does not indicate that the Examiner has acknowledged the claim for foreign priority, in the "Detailed Action" section of the Office Action, the Examiner has nevertheless acknowledged that this application is entitled to the priority of both PCT/JP04/18499, filed December 10, 2004, and JP Appl. No. 2003-415733, filed December 12, 2003.

III. Information Disclosure Statement

The Office Action of January 25, 2010, returned a copy the Form-1449 filed August 5, 2009, but the Examiner inadvertently entered his signature in the block titled "Date Considered" on page 4 of Form PTO-1449. In the Response filed July 23, 2010, Applicants drew the Examiner's attention to this error and requested that the Examiner send a signed and dated copy of page 4 of the Form PTO-1449 (see, page 6 of Response under "Information Disclosure Statements"). The present Office Action states, in relevant part, that "Regarding the IDS paper filed on August 5, 2009, page 4 is not signed" (emphasis supplied). In fact, the IDS paper filed on August 5, 2009, page 4 was both signed and dated and was returned with the present Office

Action. It appears that the "not" was intended to read "now." The Examiner is respectfully requested to confirm for the record that the references cited on page 4 of the IDS filed on August 5, 2009, were indeed considered.

Applicants also wish to clarify that, after Desig ID 188 on page 10 of the Form PTO-1449 filed on August 5, 2009 was crossed out, this document was resubmitted in an PTO/SB/08a form filed July 23, 2010 (*see*, Cite 1). This document was considered and an initialed copy of the PTO/SB/08a form was returned with the present Office Action.

Applicants respectfully request that the Examiner consider the references cited in the new Form PTO-1449 being filed with the present Amendment and Request for Continued Examination and that an initialed copy be returned with the next Official Communication.

IV. Rejection Under 35 U.S.C. § 102(e)

Claims 15-24[1] are rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Fukushima et al. (US PG Pub. No. 2004/0242847) ("Fukushima"). See, Office Action at pages 5-6.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987). Applicants assert that Fukushima fails to teach each and every element of Applicants' claims for the reasons described below.

Independent claim 15, as presently amended, is drawn to a method of screening comprising providing a plurality of different whole antibodies that bind to a given antigen, wherein the plurality of different whole antibodies comprises antibodies with weak or undetectable agonistic activity for the antigen. This method further comprises producing a minibody form of each whole antibody; screening the minibodies for their ability to agonize the antigen; and selecting a minibody if it exhibits agonistic activity greater than that of its respective whole antibody.

[1] In the introductory paragraph at page 5, the Office Action states, in relevant part, that "Claims 15-17, 19-22 and 24 are rejected...." However, the body of the rejection suggests that the Examiner intended to reject claims 15-24. Accordingly, Applicants have addressed this rejection as relating to claims 15-24.

Based on the comments on pages 7-8 of the Office Action addressing the arguments filed in the last filed Response, Applicants understand the Examiner to agree to the novelty of the presently amended claim 15. For the Examiner's convenience and for purposes of a complete record, Applicants present the arguments that were made in the last Response which are applicable here.

To be clear, independent claim 15 is drawn to methods that require "a plurality of different whole antibodies that bind to a given antigen [i.e., all of the antibodies of the plurality bind to the same antigen], wherein the plurality of whole antibodies comprises antibodies with weak or undetectable agonistic activity for the antigen." In other words, while each of the antibodies binds to the given antigen, they are not all capable of agonizing the antigen to a significant degree. At least some of the antibodies of the plurality must agonize the antigen only weakly, or not at all.

Fukushima describes experiments with three different whole antibodies, two of which (12B5 and 12E10) bind to MPL and another of which (MABL-2) binds to a different antigen, CD47. Of the three disclosed antibodies, the only "plurality of different whole antibodies that bind to a given antigen" (as required by claim 15) is the "plurality" made up of 12B5 and 12E10, both of which bind MPL. Fukushima discloses that one (and only one) of those two whole antibodies has weak or undetectable agonistic activity for MPL. (*See*, Fukushima at ¶ [0369] and Fig. 58, which show that the whole antibody 12E10 IgG has undetectable agonistic activity for MPL; and at ¶ [0325] and Fig. 51, which show that the other whole antibody, 12B5 IgG, has strong agonistic activity for MPL.) Since Fukushima's "plurality" of two anti-MPL antibodies includes only <u>one</u> antibody with weak or undetectable agonistic activity for the antigen, it does not meet the claim 15 requirement "wherein the plurality of **<u>different</u>** whole antibodies comprises antibodies with weak or undetectable agonistic activity for the antigen." Fukushima discloses no other plurality of different whole antibodies that bind to a given antigen. Thus, claim 15 is novel over the prior art.

Claims 16 to 24 depend from claim 15 and therefore are also novel for at least the same reasons. Applicants note that several dependent claims include other limitations that further distinguish over Fukushima.

For example, the list of antigens in claim 18 does not include MPL (a thrombopoietin receptor), the antigen to which Fukushima's antibodies 12B5 and 12E10 bind, or CD47 (referred to in Fukushima as "Integrin Associated Protein," or IAP), the antigen to which Fukushima's MABL-2 binds. While Fukushima does provide a list of other receptor antigens at ¶ [0044] and, as noted in the Office Action at page 5, mentions LIF receptor at [0035], no antibodies binding to any of those receptors and having what could be characterized as "weak or undetectable agonistic activity for the antigen" are disclosed. The Examiner is reminded that the screening method recited in claim 15 from which claim 18 depends requires "providing a plurality of different whole antibodies that bind to a given antigen, wherein the plurality of different whole antibodies comprises antibodies with weak or undetectable agonistic activity for the antigen." Thus, claim 18 further distinguishes over Fukushima.

Claim 23 specifies that the agonistic activities of the whole antibodies are not assayed prior to the step of producing a minibody of each whole antibody. The Office Action at page 8 points to ¶¶ [0324] and [0325] and says that "Fukushima performs side-by-side assays on each whole antibody and its minibody forms. Thus, the agonistic activity of the whole antibody is performed after the minibody is formed so that side-by-side assays are performed to compare the agonistic activities" (emphasis added). Applicants submit that this statement in the Office Action does not address the limitation of claim 23 at issue. Whether or not Fukushima assayed the whole antibody after the minibody was formed is irrelevant, as the whole antibody could, in theory, have been assayed both before and after, in which case the method would not meet the criteria of claim 23. Insofar as Applicants can ascertain, the reference is silent on the question of whether any of the whole antibodies was also tested for its agonist activity prior to producing minibody versions of the whole antibody. Silence on this question is not a "teaching" one way or the other about whether the agonist activity was determined before the minibodies were made. Nor can one assume that claim 23's limitation is "inherent" in Fukushima's methods, as it is equally plausible that the agonist activity was indeed previously determined by Fukushima (or someone else), and simply not reported in Fukushima. Under U.S. law, inherent anticipation requires that any claim limitation not explicitly found in the reference have been necessarily inherently present in the method disclosed in the reference. A mere possibility is not sufficient. As Fukushima does not disclose the limitation of claim 23, this claim is clearly not anticipated.

Claim 24 requires that the plurality of different whole antibodies be together in a mixture. In contrast, Fukushima describes handling antibodies separately (*see,* Examples 6, 7, and 8 for MABL-2, 12B5, and 12E10, respectively). Thus, claim 24 further distinguishes over Fukushima's methods.

In view of the foregoing, Applicants submit that Fukushima does not anticipate the presently claimed methods and ask that the rejection be withdrawn and the claims allowed.

V. Rejection For Nonstatutory Obviousness-Type Double Patenting

Claims 15-24 are provisionally rejected on the ground of alleged nonstatutory obviousness-type double patenting over claims 40-42, 55, and 59 of co-pending U.S. Appl. No. 10/582,413. *See*, Office Action, pages 3-4.

Without acquiescing to this rejection, Applicants respectfully request that this rejection be held in abeyance until such time as the Examiner indicates allowable subject matter in this application. Applicants will address this rejection at that time.

CONCLUSION

Applicants submit that the claims under examination in this case are in condition for allowance.

Applicants petition for a three-month extension of time to respond to the outstanding Office Action. The fee in the amount of $1,110 for a three month extension of time is being paid concurrently herewith on the Electronic Filing System (EFS) by way of Deposit Account authorization. Other than the extension fee and the RCE filing fee, no additional fees are

believed due. If Applicants are mistaken, please apply any other charges or credits to Deposit Account No. 06-1050, referencing Attorney Docket No. 14875-0163US1.

Respectfully submitted,

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